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TITLE: Trial of Naltrexone and Dextromethorphan for Gulf War
Veterans Illnesses

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14. ABSTRACT Approval to begin the study from the Department of Defense Institutional Review Board was finally obtained in February 2011, after TWO years of rewriting and revising. Immediately thereafter, we began to screen patients to participate in the study. It became immediately obvious that the exclusion criteria of the Kansas case definition of Gulf War Illness, while appropriate 20 years ago, was too strict in excluding those with a list of health problems that are distinct from Gulf War Illness. Approval was then obtained to use a modified Kansas case definition, and enrollment began. It also became obvious that many with Gulf War Illness could enter either the naltrexone or dextromethorphan arm but not both. We are applying to allow subjects to enter the arm that they qualify for. The first subject was enrolled in the trial. Due to the difficulties in locating subjects, we are applying for access to the DOD manpower database to locate additional subjects.					
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INTRODUCTION

Gulf war veterans' illnesses comprise distinct clusters of symptom-defined illnesses (1,2) for which there are neither diagnostic tests nor effective treatments. Gulf war veterans had variable exposures to a number of chemicals (3), including organophosphate insecticides, pyrethrum-related insecticides, DEET, Pyridostimine bromide, smoke from oil well fires, and Sarin gas. Gulf war veterans' illnesses may reflect an inflammatory cycle involving the brain which may be a common mechanism of many neurological conditions, whether initiated by toxic exposures, infection, or trauma. In this theory, central nervous system inflammation initiated by toxic exposures and sometimes exacerbated by subsequent exposures is a component of illness hypothesized to explain the neurological manifestations. Substance P release at sensory nerve endings is an explanation for the peripheral pain manifestations of illness.

This theory suggests that novel anti-inflammatory drugs may be of benefit in symptom-defined illnesses related to a cycle of inflammation. Dr. J. S. Hong's laboratory at the National Institute of Environmental Health Sciences has demonstrated that Morphine-related analogs, including Naltrexone and Dextromethorphan, have great potency in anti-inflammation and neuroprotective effects. Naltrexone is a safe and readily available generic medication. Dextromethorphan is also a safe and readily available generic medication that is available without a prescription as a cough medication. Results from several clinical trials showed that Naltrexone is effective in several inflammation-related diseases, such as neurogenic pain, movement disorders, etc. In addition, there were no obvious side effects in patients taking this drug for six months. This project is a randomized double-blinded studies for treating ill Gulf war veterans with Naltrexone and Dextromethorphan. Laboratory tests for markers of inflammation including neurogenic inflammation will be performed pre- and post-treatment, to see if these markers are elevated and if so, to see if treatment modulates these markers.

BODY

The major accomplishment of the past year was obtaining approval from the Department of Defense Institutional Review Board (DOD IRB) to begin the study. While this may not seem a significant accomplishment, obtaining this approval proved to be a virtually impossible task. It took two years. During this two year period, the DOD IRB would takes months to review the protocol, then present the investigators with a long and complex Protocol Review Form, requesting a large number of revisions, additions, and deletions. After the objections were met and the protocol was revised, there would be another long period of review followed by requests for more revisions, additions, and deletions. With each revision, approval for the changes had to be obtained from the East Carolina University Institutional Review Board (ECU IRB) and the United States Food and Drug Administration (US FDA) because the study drug dextromethorphan required an IND number. In February of 2011, approval to begin the study was given. For the two year period, no salary support or other resources were charged to the grant so that, should approval finally be obtained, resources would be available to conduct the study.

After final approval was obtained, subjects were recruited. It immediately became obvious that the Kansas Case Definition of Gulf War Illness was much too restrictive. Formulated shortly after the Gulf War, the definition excluded almost all co-morbidities such as diabetes because these might confound a case definition of Gulf War Illness. In the interim, it has become clear that Gulf War Illness is a distinct entity and is well defined by the inclusion criteria of the case definition, so that subjects would be eligible for inclusion even if they had other health problems. In the 20 years since the Gulf War, many veterans with Gulf War Illness have developed other medical conditions but might still be helped by the study interventions. Approval was obtained to relax the exclusion criteria. The first subject was finally enrolled toward the end of this annual reporting period, and other subjects continue to be screened.

Another problem that arose was that many victims of Gulf War Illness are taking medications that exclude them from participating. For example, many of the veterans screened are on chronic opioid therapy for the widespread chronic pain which means that they cannot take naltrexone, which is an opioid antagonist, but can take dextromethorphan. Others are on serotonergic agents for a variety of indications, which have drug interactions with dextromethorphan but not naltrexone. In order to get the numbers needed, these need to be enrolled in the study for either naltrexone or dextromethorphan. A simple addition to the protocol was proposed: Subjects who are excluded from taking naltrexone but not dextromethorphan will be enrolled in the dextromethorphan arm, and subjects who are excluded from taking dextromethorphan but not naltrexone will be enrolled in the naltrexone arm. This was rejected by the DOD IRB which is requiring a full rewrite and review in order to enroll these subjects.

Given the high rate of exclusion among screened veterans, it is obvious that a wider net must be cast in order to screen enough veterans to capture those who can be enrolled. To this end, we are seeking access to the Data Request System of the Department of Defense Manpower Database. Enrollment has proven to be a much greater challenge than we anticipated.

KEY RESEARCH ACCOMPLISHMENTS

The most significant accomplishment during the past year was finally obtaining DOD IRB approval to begin the research. A number of subjects have been screened for participation, and the first subject has been enrolled. Due to the difficult regulatory hurdles, the study is just now finally getting underway.

REPORTABLE COMES

To have reportable outcomes, a number of subjects must complete the 11 month protocol. This has not occurred to date.

CONCLUSIONS

It is very difficult to get regulatory approval to conduct research, a two or more years must be allowed for this task.

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